Diagnosis in Prader-Willi syndrome

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Abstract

Thirty one patients with the putative diagnosis of Prader-Willi syndrome were reassessed clinically and by DNA analysis. Eleven patients were judged not to have Prader-Willi syndrome and 20 to have the condition. This was confirmed by DNA analysis in all but one case. The diagnosis of Prader-Willi syndrome, especially in early infancy, should be made with caution unless confirmed by molecular genetic studies.

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The Prader-Willi syndrome is known to result from loss of the paternal contribution of a critical area on chromosome 15(q11-13) which may occur either due to a microdeletion or because of unimaternal disomy. Recent studies using molecular genetic techniques have indicated that almost all clinically typical patients have a demonstrable deletion or maternal disomy.[1]

Correct diagnosis of Prader-Willi syndrome is important because of the clinical implications. The prognosis for independent existence is poor, Greenswag (1987) finding that only 2% of adults with the syndrome were able to live independently while 79% required hospital admissions after the age of 16 years.[2] There is also a high morbidity rate associated with obesity. It is extremely desirable, therefore, to diagnose patients as accurately and early as possible so that appropriate counselling may be given to the parents and dietary management initiated.

In order to judge the most efficient method of diagnosing the condition, we have assessed all known patients with a putative diagnosis of Prader-Willi syndrome in the Glasgow area both clinically and by DNA analysis.

Patients and methods

Thirty one patients with a putative diagnosis of Prader-Willi syndrome in the Glasgow catchment area were recruited. The age range was birth to 23 years and there were 19 males and 12 females. All patients were assessed in a joint clinic comprising a geneticist, neurologist, endocrinologist, psychiatrist, and dietitian. Patients were also scored using diagnostic criteria from the Prader-Willi Association.[3]

Laboratory analysis was carried out by AC. Blood was obtained from all patients and both parents, and DNA was extracted by standard methods. Southern blotting was carried out using flanking probes (ML34, IR4-3R, 3-21, and IR10-1) and probe PW71 kindly provided by Dr K Buiting.[4] Polymerase chain reaction (PCR) primers amplifying CA repeat sequences at the loci GABRβ3 and D15S11[5] were also used with PCR products resolved on 3% agarose gels.

Results

Eleven patients were judged clinically not to have Prader-Willi syndrome after review in the joint clinic. Their details are listed in table 1. Cytogenetic deletions had been thought to be present in four of these cases. Seven of the patients had been diagnosed in infancy or early childhood because of hypotonia and difficult feeding, with developmental delay in five. When seen in later childhood/adolescence, five patients showed moderate to severe mental retardation, two were of normal intelligence, and none had typical features of Prader-Willi syndrome. None of these 11 patients fulfilled criteria from the Prader-Willi Association and none were deleted or disomic on DNA analysis.

Twenty patients were judged clinically to have Prader-Willi syndrome (13 male, seven female). All patients fulfilled the criteria from the Prader-Willi Association. Of these, only three showed definite cytogenetic deletions. Fifteen of the patients were deleted for one or more probes, and four were disomic. One patient, a girl aged 19 years, showed neither deletion or disomy with flanking probes and

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Table 1 Features of patients reassessed as not having Prader-Willi syndrome

Patient No	*DNA*	*Chromosomes*	*Presentation*	*Reassessed*
1	N/D	?Del in some	Developmental delay, not tube fed, no cry	History atypical
2	N/D	N	Obese, tube fed, hypogonadal	History atypical
3	N/D	?Del	At age 16 months hypotonic, developmental delay	Hyperactive, MR, not obese
4	N/D	N	Floppy, tube fed, developmental delay	History atypical
5	N/D	Del	Floppy, tube fed, abnormal cry	Not obese, normal intelligence
6	N/D	N	Floppy, tube fed, developmental delay, abnormal cry	MR, abnormal CT
7	N/D	Del	Floppy, tube fed, fits, hypogonadal	MR, abnormal CT
8	N/D	N	Floppy, hypogonadal, not tube fed	Normal intelligence
9	N/D	N	Floppy, hypogonadal, good feeder	Tall, MR, not obese
10	N/D	Inv dup 15*	Developmental delay, obesity, behavioural problems	MR, lacks speech ? autistic
11	N/D	tX; 15†	Slow, hypogonadal, obese	History atypical

N/D=not deleted, del=deleted on chromosomal analysis, N=normal karyotype, MR=mental retardation, CT=computed tomogram.
*Inv dup 15=inverted duplication of 15.
†tX; 15=translocation between X and 15.

Table 2 Informativeness (parental origin of deleted 15 ascertainable) of probes/primers used

Probe (locus)	*No informative*	*% Informative*
ML34 (D15S9)	1/20	5
IR4-3R (D15S11)	7/20	35
4-3RCA PCR (D15S11)	7/13	54
PW71 (D15S63)	20/20	100
3-21 (D15S10)	3/20	15
GABRβ3 PCR	15/19	79
IR10-1 (D15S12)	5/18	28

CA repeat markers and showed both bands using PW71. Although fulfilling the criteria for Prader-Willi syndrome, she has some unusual features with small but abnormal looking hands and had a loud cry at birth.

Phenotypically, there appeared to be no differences between deleted and disomic patients. However, there did appear to be some differences between males and females as regards puberty with all three pubertal girls (aged 19 years) having completed puberty spontaneously but with oligomenorrhoea later, whereas of the six boys of pubertal age (15, 16, 18, 19, 19, and 15 years respectively) only four showed early spontaneous puberty and none had completed puberty. One other patient was 23 years old and was anorchic.

Probe PW 71 was found to be the most informative and does not require parental blood. The CA repeat markers also proved highly informative and gave rapid results (table 2). The flanking probes gave no further information but were useful in confirming disomy.

Discussion

This study has shown a good correlation between the clinical and laboratory diagnosis of Prader-Willi syndrome. The clinical diagnosis is made on the characteristic presentation in the neonatal period followed by the classical progression of signs and symptoms through infancy, childhood, and adolescence.[6] Given that several patients who did not have Prader-Willi syndrome in this study were floppy at birth, required tube feeding and showed developmental delay, we would counsel against making a dogmatic diagnosis of Prader-Willi syndrome in the neonatal period, unless DNA analysis is confirmatory. Although of major importance in terms of management, the combination of obesity, hyperphagia, and developmental delay can be non-specific if not preceded by hypotonia in infancy with difficulty feeding and initial failure to thrive. Other consistent diagnostic features include a typical temperamental profile, characterised by proneness to outbursts of rage, unusual picking and scratching, and strengths in puzzle solving and visual organisation skills.[6 7]

The Prader-Willi Association criteria were useful and concurred fully with the opinion of the specialists involved in the clinic. However, we found the typical facies difficult to score objectively and there was an impression that the phenotype changed with recombinant growth hormone treatment (notably growth of the hands and feet).

Four patients who did not have Prader-Willi syndrome were thought on cytogenetic analysis to have deletions but showed no deletions on DNA analysis. This phenomenon has been previously described.[6]

In this study we did not use fluorescence in situ hybridisation. This technique is a good screening method for deletions but it will not identify disomy which comprise 20% of cases.

We have shown in this study that Prader-Willi syndrome is best diagnosed clinically by experienced clinicians or with the aid of the Prader-Willi Association criteria, backed by DNA analysis. Conventional cytogenetic analysis should not be used for the definitive diagnosis of Prader-Willi syndrome but remains useful in screening for rearrangements or translocations.

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